How CBER Evaluates Post-Licensure Adverse Events

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Post licensure Safety Surveillance

- (=Postmarketing surveillance)
- Why do it?
  - Prelicensure trials limitations
    - **size**
    - **duration**
    - **patient population: age, comorbidity, severity**
    - **exclusions**

Mission, Division of Epidemiology

- To rapidly detect and rigorously research safety problems for licensed biological products, and to facilitate appropriate regulatory, risk communication and risk management actions to mitigate these problems. DE also provides consultation to meet epidemiologic needs of CBER

Terminology

- Adverse Event vs. Reaction
- Incidence Rates vs. Reporting Rates
- Passive Surveillance = Spontaneous Reporting

21 CFR 600.80

- New version under preparation
- For manufacturers
- 15-day Alert reports
  - "Serious"
  - Unexpected
- Periodic adverse experience reports
- 21CFR 600.81 Distribution Reports

21 CFR 600.80

- “Each periodic report shall contain: A narrative summary and analysis of the information in the report and an analysis of the 15-day reports…”

AERS (MedWatch) and VAERS

- Brief, simple forms
- Direct reports
- Manufacturer Reports
- Computerized databases
- Contractor

Passive Surveillance Systems: Weaknesses

- Missing or inaccurate data
- Underreporting
- Lack of controls
- Lack of accurate “denominator”
- Near inability to assess causality
- Detection of events with long latency

Knee-Jerk Dismissal of Signal from Spontaneous Reports

- Poor quality, not “hard data”
- Not shown in clinical trials
- Adverse event not biologically plausible
- Just a background event
- Reporting rate < Background incidence rate
- Don’t impugn a great product!

Passive Surveillance Systems: Strengths

- Detect rare adverse events
- Timely availability of data
- National (and International) Coverage
- Lot-specific safety assessment
- Hypothesis generation

AERS

- CDER & CBER
- Non-vaccine biologics
- Medwatch Form
- Mostly serious reports
- 15-20K reports/year
- Adults predominate

VAERS

- CDC & CBER
- Vaccines
- VAERS Form
- Mostly non-serious
- 10-15K reports/year
- Many infants, children

First Line Screening of Serious VAERS Reports

- Contractor data entry
- Contractor follow-up nurses
- FDA: Medical Officer review
- FDA “lot” meeting

Definition of Signal, WHO

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously."

- Edwards & Biriell, Drug Safety 1994;10:93

Definitions of Signal from Waller & Lee, 1999

- Alert from any source that a drug may be associated with a previously unrecognized hazard…
- In practice: Something, that if found to be drug-related, would be considered clinically important and might impact on patient management…
- A series of cases of similar suspected adverse reactions...

MDB Stephens' Survey

- "Of 25 companies surveyed, 11 had no definition for what comprised a signal and of the remaining 14, six used increased frequency and nine [sic] used unexpected cases."

Components of a Signal

- Adverse Event Data
- Hypothesis
  - Transmitter
  - Receiver

Transmitters and Receivers of Signals:

- Consumers
- Activists
- Clinicians
- Scientists
- Pharmacovigilance staff
- Pharmaceutical manufacturers
- Politicians
- Communications Media
- Any person or group

General Approach

- Select and review relevant case reports
- Preliminary causality assessment
- Formulate hypothesis
- Search and review literature
- Preliminary causality assessment, again
- Identify further needed data

Signal Amplification Examples

- Individual adverse event report review
- PSURs, Periodic Reports
- Scientific publications
- “Data mining”
- Information requests
- Publicity

A signal may seem to be “in the eye of the beholder”

- Whose assessment is paramount?
- What criteria are used to assess the signal?
- Which signal is more important?
- Is action needed?

Fundamental Problem in Assessing Spontaneous Reports

- VAERS ~10-15K reports / year
- AERS ~15-20K reports /year (CBER)
- How can a sensitive system to detect potential product problems not be overloaded and overwhelmed by information to which we have to respond?

Filtration of Massive Number of Adverse Event Reports:

- Seriousness
- Number of reports
- Newness: in label? in literature?
- reporting rates vs. background rates
- GPS-EBGM, Proportional reporting ratios
- Clinical Trials, other studies

VAERS

- National Childhood Vaccine Injury Act 1986
- VAERS Established 1990
- CDC & FDA

How many reports to generate an hypothesis?

- Wide range of possibilities
- As few as one (eg, positive rechallenge)
- 3+ for relatively rare events
- Relates to “background rate of adverse event of interest

Rotavirus Vaccine-Intussusception

- Clinical Trials Signal
- Wild type RV & intussusception study
- FDA - licensure
- CDC - recommendations for use
- Post-marketing Surveillance (VAERS)
- Background rates
- Population-based incidence rates
- Withdrawal

Elusive Background Rates

- Say we have X occurrences of event Y,
- What is the expected number of events?
- Medical Literature, sometimes has them
  - Generalizability?
  - Subgroups
- Other sources
- For X, how high is high?
- Example: intussusception and RV vaccine

Important Characteristics RV- Intussusception

- Age
- Dose
- Severity
- Acute onset
- Interval from vaccination to intussusception

Alopecia after Vaccination

- Telephone call to FDA from parent
- Positive rechallenge
- Additional reports in VAERS
- Not a “serious” adverse event

The Value of Case Series: MMWR, June 5, 1981

- 5 cases PCP pneumonia, 2 died
- “Homosexuals”
- Previously healthy
- Editorial
  - “cellular immune dysfunction related to a common exposure”
  - “disease acquired through sexual contact”

“Data Mining”

- Weights signals
- Empirical Bayesian Geometric Mean
- EBGM algorithm (ATT Labs)
- Implementation in progress:
  - FDA AERS
  - FDA VAERS
  - CDC VAERS

Causality Determination is Part of Signal Filtration

- Biologic plausibility
- Temporal association
  - Time to onset
  - Rechallenge, Dechallenge
- Dose-response
- Strength of association
- Specificity
- Analogy
- Consistency of data
- Alternative explanations

Contribution of Prelicensure Staff in investigating & evaluating adverse events

- Specific product expertise
- Knowledge of clinical trials
- Specific subject area expertise
- Package insert experience

Signal's Importance to us Depends on:

- Health impact
- Effective Intervention possible?
- Causality assessment (preliminary)
- Basic science considerations
- Work we devote to it

Lingering Vaccine-AE Signals

- Gulf War Syndrome
- Rheumatologic condition
  - Arthritis
- Neuro-psychiatric condition
  - Autism
  - Cognitive dysfunction

Hard-to-Dismiss Signals

- Chronic disease
- Unknown cause
- Insidious onset
- Exposure-onset interval unclear
- “Subjective” complaints
- Ill-defined disease
- REAL DRUG REACTIONS!

Deciding on Response to Signals

- Public Health
- Cost
- Scientific

Adverse Event Responses

- Evaluation of Signals
- Change to Package Insert (“Label”)
- “Dear Doctor Letter”
- Professional Mtg Presentations/Abstracts
- Peer-reviewed Publications
- Risk Management Program
- Product Withdrawal